IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 6799**
Seishi KATO et al.	:	Docket No. 2002-0400A
Serial No. 10/088,859	:	Group Art Unit Not Yet Assigned
Filed May 29, 2002	:	Examiner Not Yet Assigned
A METHOD FOR PRODUCING AN ANTIBODY BY GENE IMMUNIZATION	:	THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents,
Washington, D.C. 20231

Sir:

Responsive to the Notice dated May 30, 2002, please amend the above-identified application as follows:

In the Specification:

Page 1, line 1, delete the entire heading.

between lines 3 and 6, insert the following heading:

BACKGROUND OF THE INVENTION

line 6, replace the heading with the following new heading:

1. Field of the Invention

line 15, replace the heading with the following new heading:

2. Description of the Related Art

Page 2, replace the paragraph beginning at line 22 with the following paragraph:

The purpose of the invention of the present application is to provide a method for producing antibodies to proteins, which were difficult to produce using presently known gene immunization methods.

line 31, replace the heading with the following new heading:

Summary of the Invention

Page 4, between lines 4 and 7, insert the paragraph in Appendix A attached herewith.

line 7, replace the heading with the following new heading:

Description of the Preferred Embodiments

Page 6, replace the paragraph beginning at line 12 with the following paragraph:

The following examples serve to illustrate the invention in more detail but are not intended as a limitation thereof. In these examples, basic procedures for recombination of DNA and enzyme reactions are carried out according to the articles, "Molecular Cloning; A laboratory manual", Cold Spring Harbor Laboratory, 1989. Restriction enzymes and a variety of modified enzymes were obtained from Takara Shuzo Co., Ltd., unless otherwise stated. The compositions of buffer solutions in respective enzyme reactions and the reaction conditions were set according to the specification attached.

Page 10, delete line 1 in its entirety.

replace the paragraph beginning at line 3 with the following paragraph:

According to the present invention, an antibody against an antigenic protein, which was difficult to produce using presently known gene immunization, can be produced. The result is an antibody useful as drugs, diagnostic agents, and reagents for research.

In the Abstract:

Page 12, line 1, replace the heading with the following new heading:

ABSTRACT OF THE DISCLOSURE

replace the paragraph beginning at line 3 with the following paragraph:

The present invention of the application provides a method for producing an antibody which comprises inoculating an expression vector expressing a fusion protein to an animal, and isolating and purifying an antibody against an antigenic protein from the animal, wherein the fusion protein is an antigenic protein fused to the C-terminal side of a transmembrane domain in which the N-terminal side is located in the cell and the C-terminal is out of the cell. According to the present invention, an antibody against an antigenic protein, which was difficult to produce using presently known gene immunization, can be produced. The result is an antibody useful as drugs, diagnostic agents, and reagents for research.

In the Sequence Listing:

Please replace the Sequence Listing of record with the attached substitute Sequence Listing.

In the Claims:

Above claim 1, insert the following:

What is claimed is:

REMARKS

The foregoing amendments are presented to place the application in compliance with the sequence rules under 37 CFR 1.821-1.825.

Applicants have submitted a Sequence Listing in both paper and computer readable form as required by 37 C.F.R. 1.821(c) and (e). Amendments directing its entry into the specification have also been incorporated herein. The content of the paper and computer readable copies are the same and no new matter has been added.

The specification has also been carefully reviewed and editorial changes have been effected. All of the changes are minor in nature and therefore do not require extensive discussion. Specifically, the specification headings have been amended in conformance with U.S. practice.

Also, the amino acid sequences disclosed in Figure 4 which represent portions of SEQ ID Nos: 9-13 have been identified and labeled in the Brief Description of the Drawings (See Appendix A) in accordance with U. S. practice.

With regard to the Notice also requesting that an executed Oath and Declaration be submitted, Applicants wish to note that an executed Oath and Declaration was submitted on May 29, 2002. A copy of the submitted executed Declaration is enclosed herewith along with the cover letter (indicating the filing of the executed Declaration). Applicants respectfully request that the

Patent Office review the application papers to ensure that the executed Declaration is present in the file.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

In view of the foregoing, it is believed that each requirement set forth in the Notice has been satisfied, and that the application is now in compliance with the sequence rules under 37 CFR 1.821-1.825. Accordingly, favorable examination on the merits is respectfully requested.

Respectfully submitted,

Seishi KATO et al.

By:_____

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Registration No. 40,949
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June 28, 2002

APPENDIX A

The amino acid sequence of HP01347 shown in Figure 4 corresponds to amino acid residues 1-72 of SEQ ID No: 9. The amino acid sequence of HP10328 shown in Figure 4 corresponds to amino acid residues 1-128 of SEQ ID No: 10. The amino acid sequence of HP10390 shown in Figure 4 corresponds to amino acid residues 1-50 of SEQ ID No:11. The amino acid sequence of HP10433 shown in Figure 4 corresponds to amino acid residues 1-135 of SEQ ID No: 12. The amino acid sequence of HP10481 shown in Figure 4 corresponds to amino acid residues 1-148 of SEQ ID No: 13.

[redacted]

Version with Markings to Show Changes Made

~~DESCRIPTION~~

A Method for producing an Antibody by Gene Immunization

BACKGROUND OF THE INVENTION

1. ~~Technical~~ Field of the Invention

The invention of the present application relates to a method for producing an antibody by gene immunization. More specifically, the invention relates to a method of enabling easy production of an antibody useful as drugs, diagnostic agents, reagents for the research, and etc., and to an expression vector used in this method.

2. Description of the Related ~~Background~~ Art

An antibody has widely been utilized as reagents for the research for the purpose of detection, purification, elimination, inhibition of a protein or the like, because it has property of recognizing specific protein and binding thereto. Recently, it has widely been used not only as reagents for the research but also as drugs or diagnostic agents.

In producing antibodies, it has so far been general to use a method that a large amount of protein as an antigen is purified and injected to an animal or animals such as rabbits or mice to collect antibodies generated in sera. It required, however, much time and a great deal of labor to obtain a large amount of a purified antigenic protein. It is desired to provide a more convenient method for producing antibodies, accordingly.

Recently, it was reported that when a gene coding for an influenza virus nucleoprotein is integrated into an expression vector

and intramuscularly injected directly as DNA to mice, then virus proteins are produced in the murine bodies and additionally the antibody against these proteins are generated in the sera. (Ulmer et al., Science 259: 1745-1749, 1993; Ginsbert et al., "Vaccines 93"). As a result, this expression vector received much attention as a new type of vaccine, that is, DNA vaccine, since mice have acquired immunity to virus. Thus, it has been designated as gene immunization that an expression vector for an antigenic protein is inoculated directly to an animal to generate immunity. In using gene immunization, however, in some cases, the titer of the generated antibody is very low or no antibody is generated depending on the kind of the antigen used.

It was reported as an example of gene immunization that ovalbumin was fused in the downstream of transmembrane domain of transferrin receptor to form a membrane type and it was injected intramuscularly or subcutaneously to mice in order to investigate an effect of the expression site of antigenic protein on the efficacy of gene immunization. The titer of the antibodies generated, however, rather decreased since the protein was converted into a membrane type. (Boyle et al., Int. Immunol. 9: 1897-1906, 1997).

The purpose of the invention of present application is to provide a method for producing antibodies to proteins, which ~~it was~~ were difficult to produce ~~in so far~~ using presently known gene immunization methods.

Additionally, the purpose of the invention is to provide an expression vector used in the above-mentioned method for producing an antibody.

~~Disclosure~~ Summary of the Invention

The present application, as the invention for solving the

Fig. 4 shows the respective N-terminal amino acid sequences of fusion proteins comprising urokinase and transmembrane domains in a variety of membrane proteins.

- Insert "Appendix A"

Description of the Preferred Embodiments

~~Best Mode for Carrying Out the Invention~~

In a method for producing antibodies according to the invention, the expression vector to be inoculated to animals may be constructed as an expression vector having a fusion polynucleotide that consists of a polynucleotide encoding an antigenic protein and a polynucleotide encoding a transmembrane domain.

As for an antigenic protein, any one that can generate an antigen-antibody reaction in vivo may be used. The polynucleotide encoding an antigenic protein may be any one of genomic DNA, cDNA, synthetic DNA, etc., as far as it has an open reading frame (ORF). When the antigenic protein is an inherent secretory protein, it is used after removal of the signal sequence peptide originally possessed by the protein.

As for the transmembrane domain, any domain may be used as far as its N-terminal side is in the cell and the C-terminal side is out of the cell. For example, transmembrane domains of type II-membrane proteins or those of multispan-type membrane proteins may be used. The proteins that an antigenic protein is fused to the C-terminal side of these transmembrane domains take forms that the antigenic protein portion exists on the surface of the cell membrane. As for the transmembrane domain, for example, that of human type-II membrane protein HP10085 (SEQ ID NO: 2) may be used. In this case, the transmembrane domain to be fused with an antigenic protein is a polypeptide containing at least 1st methionine (Met) to 26th lysine (Lys)

immunoassay (ELISA), Western blotting, immuno-precipitation, antibody staining, and the like may be used. After confirmation of the presence of the antibody in the serum by these methods, the serum may be used as a polyclonal antibody specimen as it is or may be purified by affinity column chromatography to yield IgG. Alternatively, the spleen may be taken out from the animal acquiring immunity and the monoclonal antibody can be produced in a conventional manner.

Examples

The following examples serve to illustrate the invention in more detail ~~and specifically~~ but are not intended as a limitation thereof. In these examples, basic procedures for recombination of DNA and enzyme reactions are carried out according to the articles, "Molecular Cloning; A laboratory manual", Cold Spring Harbor Laboratory, 1989. Restriction enzymes and a variety of modified enzymes were obtained from Takara Shuzo Co., Ltd., unless otherwise stated. The compositions of buffer solutions in respective enzyme reactions and the reaction conditions were set according to the specification attached.

(1) Construction of an Expression Vector for the Urokinase-Fusion Protein

When urokinase is used as an antigenic protein, 3 kinds of expression vectors were used, that is, for secretion expression, for membrane form expression, and for intracellular expression. That is, the following vectors were respectively used: for secretion expression, pSSD1-UPA22 which expresses the signal sequence and protease domain of urokinase (Yokoyama-Kobayashi et al., Gene 163: 193-196, 1995); for membrane form expression, pSSD3-10085H which expresses a protein prepared by fusing a sequence from the N-terminal side to the

~~Industrial Applicability~~

According to the present invention, an antibody against an antigenic protein, which ~~it~~ was difficult to produce ~~in the so far~~ using presently known gene immunization, can be produced. The resulting ~~ing~~ is an antibody ~~is~~ useful as drugs, diagnostic agents, and reagents for ~~the~~ research.

CLAIMS

What is claimed is:

1. A method for producing an antibody which comprises inoculating an expression vector expressing a fusion protein to an animal, isolating an antibody against an antigenic protein from the animal and purifying the antibody, wherein the fusion protein is an antigenic protein fused with the C-terminal of a transmembrane domain of which the N-terminal side is located in the cell and the C-terminal side is out of the cell.

2. The method for producing an antibody of claim 1, wherein the transmembrane domain is a polypeptide having at least the amino acid sequence from 1st to 26th of SEQ ID NO. 2.

3. An expression vector expressing a fusion protein in which an antigenic protein is fused with the C-terminal of transmembrane domain of which the N-terminal side is located in the cell and the C-terminal side is out of the cell.

4. The expression vector of claim 3, wherein the transmembrane domain is a polypeptide having at least the amino acid sequence from 1st to 26th of SEQ ID NO. 2.

ABSTRACT OF THE DISCLOSURE

The present invention of the application provides a method for producing an antibody which comprises inoculating an expression vector expressing a fusion protein to an animal, and isolating and purifying an antibody against an antigenic protein from the animal, wherein the fusion protein is an antigenic protein fused to the C-terminal side of a transmembrane domain in which the N-terminal side is located in the cell and the C-terminal is out of the cell. According to the present invention, an antibody against an antigenic protein, which ~~it~~ was difficult to produce ~~in the so far~~ known gene immunization, can be produced. The ~~resulting~~ is an antibody ~~is~~ useful as drugs, diagnostic agents, and reagents for the research.

SEQUENCE LISTING

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NAGATA, Naoki
FUJIMURA, Naoko
KOBAYASHI, Midori
ITO, Koichi
ISHIZUKA, Yoshiko

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45 50 55

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Ser Asp His Trp Ile Gly Leu Lys Met Ala Lys Asn Arg Thr Gly Gln
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105 110 115 120

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Tyr Thr Glu Arg Lys Trp Ile Cys Arg Lys Arg Ile His
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35 40 45
Phe Ser Lys Glu Glu Gly Asp Trp Asn Ser Ser Lys Tyr Asn Cys Ser
50 55 60
Thr Gln His Ala Asp Leu Thr Ile Ile Asp Asn Ile Glu Glu Met Asn
65 70 75 80
Phe Leu Arg Arg Tyr Lys Cys Ser Ser Asp His Trp Ile Gly Leu Lys
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     10                  15                  20

agt gac gtg ctg cag cgg gac ttg cga aag gtg ctg gac cat cga gac   149
Ser Asp Val Leu Gln Arg Asp Leu Arg Lys Val Leu Asp His Arg Asp
 25                  30                  35                  40

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                 45                  50                  55

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         75                  80                  85

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         35                  40                  45
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Ser Glu Leu Tyr Met Gln Val Asp Leu Gly Cys Asn Phe Phe Val Asp
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        115                 120                 125
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Val Gln Val Ser Lys Val Pro Ser Ser Leu Ser Gln Glu Gln Ser Glu
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Thr Ser Met Val Thr His Pro Asp Phe Ala Thr Gln Pro Gln His Val
65                  70                  75                  80

cag aac ttc ctc ctg tac aga cac tgc cgc cac ttt ccc ctg ctg cag   405
Gln Asn Phe Leu Leu Tyr Arg His Cys Arg His Phe Pro Leu Leu Gln
                85                  90                  95
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gac gtg ccc ccc tct aag tgc gcg cag ccg gtc ttc ctg ctg ctg gtg    453
Asp Val Pro Pro Ser Lys Cys Ala Gln Pro Val Phe Leu Leu Leu Val
            100                 105                 110

atc aag tcc tcc cct agc aac tat gtg cgc cgc gag ctg ctg cgg cgc    501
Ile Lys Ser Ser Pro Ser Asn Tyr Val Arg Arg Glu Leu Leu Arg Arg
        115                 120                 125

acg tgg ggc cgc gag cgc aag gta cgg ggt ttg cag ctg cgc ctc ctc    549
Thr Trp Gly Arg Glu Arg Lys Val Arg Gly Leu Gln Leu Arg Leu Leu
    130                 135                 140

ttc ctg gtg ggc aca gcc tcc aac ccg cac gag gcc cgc aag gtc aac    597
Phe Leu Val Gly Thr Ala Ser Asn Pro His Glu Ala Arg Lys Val Asn
145                 150                 155                 160

cgg ctg ctg gag ctg gag gca cag act cac gga gac atc ctg cag tgg    645
Arg Leu Leu Glu Leu Glu Ala Gln Thr His Gly Asp Ile Leu Gln Trp
                165                 170                 175

gac ttc cac gac tcc ttc ttc aac ctc acg ctc aag cag gtc ctg ttc    693
Asp Phe His Asp Ser Phe Phe Asn Leu Thr Leu Lys Gln Val Leu Phe
            180                 185                 190

tta cag tgg cag gag aca agg tgc gcc aac gcc agc ttc gtg ctc aac    741
Leu Gln Trp Gln Glu Thr Arg Cys Ala Asn Ala Ser Phe Val Leu Asn
        195                 200                 205

ggg gat gat gac gtc ttt gca cac aca gac aac atg gtc ttc tac ctg    789
Gly Asp Asp Asp Val Phe Ala His Thr Asp Asn Met Val Phe Tyr Leu
    210                 215                 220

cag gac cat gac cct ggc cgc cac ctc ttc gtg ggg caa ctg atc caa    837
Gln Asp His Asp Pro Gly Arg His Leu Phe Val Gly Gln Leu Ile Gln
225                 230                 235                 240

aac gtg ggc ccc atc cgg gct ttt tgg agc aag tac tat gtg cca gag    885
Asn Val Gly Pro Ile Arg Ala Phe Trp Ser Lys Tyr Tyr Val Pro Glu
                245                 250                 255

gtg gtg act cag aat gag cgg tac cca ccc tat tgt ggg ggt ggt ggc    933
Val Val Thr Gln Asn Glu Arg Tyr Pro Pro Tyr Cys Gly Gly Gly Gly
            260                 265                 270

ttc ttg ctg tcc cgc ttc acg gcc gct gcc ctg cgc cgt gct gcc cat    981
Phe Leu Leu Ser Arg Phe Thr Ala Ala Ala Leu Arg Arg Ala Ala His
        275                 280                 285

gtc ttg gac atc ttc ccc att gat gat gtc ttc ctg ggt atg tgt ctg    1029
Val Leu Asp Ile Phe Pro Ile Asp Asp Val Phe Leu Gly Met Cys Leu
    290                 295                 300

gag ctt gag gga ctg aag cct gcc tcc cac agc ggc atc cgc acg tct    1077
Glu Leu Glu Gly Leu Lys Pro Ala Ser His Ser Gly Ile Arg Thr Ser
305                 310                 315                 320
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ggc.gtg cgg gct cca tcg caa cac ctg tcc tcc ttt gac ccc tgc ttc   1125
Gly Val Arg Ala Pro Ser Gln His Leu Ser Ser Phe Asp Pro Cys Phe
                325                 330                 335

tac cga gac ctg ctg ctg gtg cac cgc ttc cta cct tat gag atg ctg   1173
Tyr Arg Asp Leu Leu Leu Val His Arg Phe Leu Pro Tyr Glu Met Leu
            340                 345                 350

ctc atg tgg gat gcg ctg aac cag ccc aac ctc acc tgc ggc aat cag   1221
Leu Met Trp Asp Ala Leu Asn Gln Pro Asn Leu Thr Cys Gly Asn Gln
        355                 360                 365

aca cag atc tac tga gtcagcatca gggtccccag cctctgggct cctgtttcca   1276
Thr Gln Ile Tyr
    370

taggaagggg cgacaccttc ctcccaggaa gctgagacct ttgtggtctg agcataaggg 1336

agtgccaggg aaggtttgag gtttgatgag tgaatattct ggctggcgaa ctcctacaca 1396

tccttcaaaa cccacctggt actgttccag catcttccct ggatggctgg aggaactcca 1456

gaaaatatcc atcttctttt tgtggctgct aatggcagaa gtgcctgtgc tagagttcca 1516

actgtggatg catccgtccc gtttgagtca aagtcttact tccctgctct cacctactca 1576

cagacgggat gctaagcagt gcacctgcag tggtttaatg gcagataagc tccgtctgca 1636

gttccaggcc agccagaaac tcctgtgtcc acatagagct gacgtgagaa atatctttca 1696

gcccaggaga gaggggtcct gatcttaacc ctttcctggg tctcagacaa ctcagaaggt 1756

tgggggggata ccagagaggt ggtggaatag gaccgccccc tccttacttg tgggatcaaa 1816

tgctgtaatg gtggaggtgt gggcagagga gggaggcaag tgtcctttga aagttgtgag 1876

agctcagagt ttctggggtc ctcattagga gcccccatcc ctgtgttccc caagaattca 1936

gagaacagca ctggggctgg aatgatcttt aatgggccca aggccaacag gcatatgcct 1996

cactactgcc tggagaaggg agagattcag gtcctccagc agcctccctc acccagtatg 2056

ttttacagat tacgggggga ccgggtgagc cagtgacccc ctgcagcccc cagcttcagg 2116

cctcagtgtc tgccagtcaa gcttcacagg cattgtgatg gggcagcctt ggggaatata 2176

aaattttgtg                                                        2186
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<210> 11
<211> 814
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (145)..(693)

<400> 11
agaatcccgg acagccctgc tccctgcagc caggtgtagt ttcgggagcc actggggcca 60

aagtgagagt ccagcggtct tccagcgctt gggccacggc ggcggccctg ggagcagagg 120

tggagcgacc ccattacgct aaag atg aaa ggc tgg ggt tgg ctg gcc ctg 171
Met Lys Gly Trp Gly Trp Leu Ala Leu
1 5

ctt ctg ggg gcc ctg ctg gga acc gcc tgg gct cgg agg agc cag gat 219
Leu Leu Gly Ala Leu Leu Gly Thr Ala Trp Ala Arg Arg Ser Gln Asp
10 15 20 25

ctc cac tgt gga gca tgc agg gct ctg gtg gat gaa cta gaa tgg gaa 267
Leu His Cys Gly Ala Cys Arg Ala Leu Val Asp Glu Leu Glu Trp Glu
30 35 40

att gcc cag gtg gac ccc aag aag acc att cag atg gga tct ttc cgg 315
Ile Ala Gln Val Asp Pro Lys Lys Thr Ile Gln Met Gly Ser Phe Arg
45 50 55

atc aat cca gat ggc agc cag tca gtg gtg gag gtg cct tat gcc cgc 363
Ile Asn Pro Asp Gly Ser Gln Ser Val Val Glu Val Pro Tyr Ala Arg
60 65 70

tca gag gcc cac ctc aca gag ctg ctg gag gag ata tgt gac cgg atg 411
Ser Glu Ala His Leu Thr Glu Leu Leu Glu Glu Ile Cys Asp Arg Met
75 80 85

aag gag tat ggg gaa cag att gat cct tcc acc cat cgc aag aac tac 459
Lys Glu Tyr Gly Glu Gln Ile Asp Pro Ser Thr His Arg Lys Asn Tyr
90 95 100 105

gta cgt gta gtg ggc cgg aat gga gaa tcc agt gaa ctg gac cta caa 507
Val Arg Val Val Gly Arg Asn Gly Glu Ser Ser Glu Leu Asp Leu Gln
110 115 120

ggc atc cga atc gac tca gat att agc ggc acc ctc aag ttt gcg tgt 555
Gly Ile Arg Ile Asp Ser Asp Ile Ser Gly Thr Leu Lys Phe Ala Cys
125 130 135

gag agc att gtg gag gaa tac gag gat gaa ctc att gaa ttc ttt tcc 603
Glu Ser Ile Val Glu Glu Tyr Glu Asp Glu Leu Ile Glu Phe Phe Ser
140 145 150

cga gag gct gac aat gtt aaa gac aaa ctt tgc agt aag cga aca gat 651
Arg Glu Ala Asp Asn Val Lys Asp Lys Leu Cys Ser Lys Arg Thr Asp
155 160 165

ctt tgt gac cat gcc ctg cac ata tcg cat gat gag cta tga 693
Leu Cys Asp His Ala Leu His Ile Ser His Asp Glu Leu
170 175 180

accactggag cagcccacac tggcttgatg gatcaccccc aggaggggaa aatggtggca 753

atgcctttta tatattatgt ttttactgaa attaactgaa aaaatatgaa accaaaagta 813

c 814

<210> 12
<211> 695
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (73)..(564)

<400> 12
aagatttcag ctgcgggacg gtcaggggag acctccaggc gcagggaagg acggccaggg 60

tgacacggaa gc atg cga cgg ctg ctg atc cct ctg gcc ctg tgg ctg ggc 111
Met Arg Arg Leu Leu Ile Pro Leu Ala Leu Trp Leu Gly
1 5 10

gcg gtg ggc gtg ggc gtc gcc gag ctc acg gaa gcc cag cgc cgg ggc 159
Ala Val Gly Val Gly Val Ala Glu Leu Thr Glu Ala Gln Arg Arg Gly
15 20 25

ctg cag gtg gcc ctg gag gaa ttt cac aag cac ccg ccc gtg cag tgg 207
Leu Gln Val Ala Leu Glu Glu Phe His Lys His Pro Pro Val Gln Trp
30 35 40 45

gcc ttc cag gag acc agt gtg gag agc gcc gtg gac acg ccc ttc cca 255
Ala Phe Gln Glu Thr Ser Val Glu Ser Ala Val Asp Thr Pro Phe Pro
50 55 60

gct gga ata ttt gtg agg ctg gaa ttt aag ctg cag cag aca agc tgc 303
Ala Gly Ile Phe Val Arg Leu Glu Phe Lys Leu Gln Gln Thr Ser Cys
65 70 75

cgg aag agg gac tgg aag aaa ccc gag tgc aaa gtc agg ccc aat ggg 351
Arg Lys Arg Asp Trp Lys Lys Pro Glu Cys Lys Val Arg Pro Asn Gly
80 85 90

agg aaa cgg aaa tgc ctg gcc tgc atc aaa ctg ggc tct gag gac aaa 399
Arg Lys Arg Lys Cys Leu Ala Cys Ile Lys Leu Gly Ser Glu Asp Lys
95 100 105

gtt ctg ggc cgg ttg gtc cac tgc ccc ata gag acc caa gtt ctg cgg 447
Val Leu Gly Arg Leu Val His Cys Pro Ile Glu Thr Gln Val Leu Arg
110 115 120 125

gag gct gag gag cac cag gag acc cag tgc ctc agg gtg cag cgg gct 495
Glu Ala Glu Glu His Gln Glu Thr Gln Cys Leu Arg Val Gln Arg Ala
130 135 140

ggt gag gac ccc cac agc ttc tac ttc cct gga cag ttc gcc ttc tcc 543
Gly Glu Asp Pro His Ser Phe Tyr Phe Pro Gly Gln Phe Ala Phe Ser
145 150 155

aag gcc ctg ccc cgc agc taa gccagcactg agctgcgtgg tgcctccagg 594

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Lys Ala Leu Pro Arg Ser
        160

accgctgccg gtggtaacca gtggaagacc ccagccccca gggagaggac cccgttctat 654

ccccagccat gataataaag ctgctctccc agctgcctct c                     695


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<211> 1451
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (105)..(1436)

<400> 13
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gcccgctcca tggcggtgga tgcctgactg gaagcccgag tggg atg cgg ctg acg  116
                                                Met Arg Leu Thr
                                                  1

cgg aag cgg ctc tgc tcg ttt ctt atc gcc ctg tac tgc cta ttc tcc   164
Arg Lys Arg Leu Cys Ser Phe Leu Ile Ala Leu Tyr Cys Leu Phe Ser
  5                  10                  15                  20

ctc tac gct gcc tac cac gtc ttc ttc ggg cgc cgc cgc cag gcg ccg   212
Leu Tyr Ala Ala Tyr His Val Phe Phe Gly Arg Arg Arg Gln Ala Pro
                 25                  30                  35

gcc ggg tcc ccg cgg ggc ctc agg aag ggg gcg gcc ccc gcg cgg gag   260
Ala Gly Ser Pro Arg Gly Leu Arg Lys Gly Ala Ala Pro Ala Arg Glu
             40                  45                  50

aga cgc ggc cga gaa cag tcc act ttg gaa agt gaa gaa tgg aat cct   308
Arg Arg Gly Arg Glu Gln Ser Thr Leu Glu Ser Glu Glu Trp Asn Pro
         55                  60                  65

tgg gaa gga gat gaa aaa aat gag caa caa cac aga ttt aaa act agc   356
Trp Glu Gly Asp Glu Lys Asn Glu Gln Gln His Arg Phe Lys Thr Ser
     70                  75                  80

ctt caa ata tta gat aaa tcc acg aaa gga aaa aca gat ctc agt gta   404
Leu Gln Ile Leu Asp Lys Ser Thr Lys Gly Lys Thr Asp Leu Ser Val
 85                  90                  95                 100

caa atc tgg ggc aaa gct gcc att ggc ttg tat ctc tgg gag cat att   452
Gln Ile Trp Gly Lys Ala Ala Ile Gly Leu Tyr Leu Trp Glu His Ile
                105                 110                 115

ttt gaa ggc tta ctt gat ccc agc gat gtg act gct caa tgg aga gaa   500
Phe Glu Gly Leu Leu Asp Pro Ser Asp Val Thr Ala Gln Trp Arg Glu
            120                 125                 130

gga aag tca atc gta gga aga aca cag tac agc ttc atc act ggt cca   548
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Gly Lys Ser Ile Val Gly Arg Thr Gln Tyr Ser Phe Ile Thr Gly Pro
        135                 140                 145

gct gta ata cca ggg tac ttc tcc gtt gat gtg aat aat gtg gta ctc   596
Ala Val Ile Pro Gly Tyr Phe Ser Val Asp Val Asn Asn Val Val Leu
    150                 155                 160

att tta aat gga aga gaa aaa gca aag atc ttt tat gcc acc cag tgg   644
Ile Leu Asn Gly Arg Glu Lys Ala Lys Ile Phe Tyr Ala Thr Gln Trp
165                 170                 175                 180

tta ctt tat gca caa aat tta gtg caa att caa aaa ctc cag cat ctt   692
Leu Leu Tyr Ala Gln Asn Leu Val Gln Ile Gln Lys Leu Gln His Leu
                185                 190                 195

gct gtt gtt ttg ctc gga aat gaa cat tgt gat aat gag tgg ata aac   740
Ala Val Val Leu Leu Gly Asn Glu His Cys Asp Asn Glu Trp Ile Asn
            200                 205                 210

cca ttc ctc aaa aga aat gga ggc ttc gtg gag ctg ctt ttc ata ata   788
Pro Phe Leu Lys Arg Asn Gly Gly Phe Val Glu Leu Leu Phe Ile Ile
        215                 220                 225

tat gac agc ccc tgg att aat gac gtg gat gtt ttt cag tgg cct tta   836
Tyr Asp Ser Pro Trp Ile Asn Asp Val Asp Val Phe Gln Trp Pro Leu
    230                 235                 240

gga gta gca aca tac agg aat ttt cct gtg gtg gag gca agt tgg tca   884
Gly Val Ala Thr Tyr Arg Asn Phe Pro Val Val Glu Ala Ser Trp Ser
245                 250                 255                 260

atg ctg cat gat gag agg cca tat tta tgt aat ttc tta gga acg att   932
Met Leu His Asp Glu Arg Pro Tyr Leu Cys Asn Phe Leu Gly Thr Ile
                265                 270                 275

tat gaa aat tca tcc aga cag gca cta atg aac att ttg aaa aaa gat   980
Tyr Glu Asn Ser Ser Arg Gln Ala Leu Met Asn Ile Leu Lys Lys Asp
            280                 285                 290

ggg aac gat aag ctt tgt tgg gtt tca gca aga gaa cac tgg cag cct   1028
Gly Asn Asp Lys Leu Cys Trp Val Ser Ala Arg Glu His Trp Gln Pro
        295                 300                 305

cag gaa aca aat gaa agt ctt aag aat tac caa gat gcc ttg ctt cag   1076
Gln Glu Thr Asn Glu Ser Leu Lys Asn Tyr Gln Asp Ala Leu Leu Gln
    310                 315                 320

agt gat ctc aca ttg tgc ccg gtc gga gta aac aca gaa tgc tat cga   1124
Ser Asp Leu Thr Leu Cys Pro Val Gly Val Asn Thr Glu Cys Tyr Arg
325                 330                 335                 340

atc tat gag gct tgc tcc tat ggc tcc att cct gtg gtg gaa gac gtg   1172
Ile Tyr Glu Ala Cys Ser Tyr Gly Ser Ile Pro Val Val Glu Asp Val
                345                 350                 355

atg aca gct ggc aac tgt ggg aat aca tct gtg cac cac ggt gct cct   1220
Met Thr Ala Gly Asn Cys Gly Asn Thr Ser Val His His Gly Ala Pro
```

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          360                 365                 370

ctg cag tta ctc aag tcc atg ggt gct ccc ttt atc ttt atc aag aac   1268
Leu Gln Leu Leu Lys Ser Met Gly Ala Pro Phe Ile Phe Ile Lys Asn
        375                 380                 385

tgg aag gaa ctc cct gct gtt tta gaa aaa gag aaa act ata att tta   1316
Trp Lys Glu Leu Pro Ala Val Leu Glu Lys Glu Lys Thr Ile Ile Leu
    390                 395                 400

caa gaa aaa att gaa aga aga aaa atg tta ctt cag tgg tat cag cac   1364
Gln Glu Lys Ile Glu Arg Arg Lys Met Leu Leu Gln Trp Tyr Gln His
405                 410                 415                 420

ttc aag aca gag ctt aaa atg aaa ttt act aat att tta gaa agc tca   1412
Phe Lys Thr Glu Leu Lys Met Lys Phe Thr Asn Ile Leu Glu Ser Ser
                425                 430                 435

ttt tta atg aat aat aaa agt taa ttatcttttt gagct                 1451
Phe Leu Met Asn Asn Lys Ser
            440
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[redacted]